Immunosuppressive Therapy in Systemic Lupus Erythematosus

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Systemic Lupus Erythematosus Therapy:

- Therapy is usually long term
- Tailored according to severity of the disease and clinical manifestations
- Ranging from:
  - Mild photosensetivity
  - Musculoskeletal manifestations.
  - Discoid lupus, severe maculopapular lesions
  - Serositis
  - Severe life threatening systemic disease
- Maintenance therapy once remission induced: Mycophenolate mofetil or azathioprine
- Refractory disease: Rituximab, IV IG

Immunotherapy

Types of Immunotherapy:

- Active immunotherapy
- Passive immunotherapy

Active immunotherapy

- It is the type of immunotherapy that attempts to stimulate the host intrinsic immune response to a disease. It includes two types:
  - Specific active immunotherapy
  - Non specific active immunotherapy

- Specific active immunotherapy :

The generation of cell mediated and antibody immune responses focused on specific antigen.

e.g. cancer vaccines, cellular therapies.

- Non specific active immunotherapy:

The generation of general immune system response using:

  - Cytokines to destroy tumor cells. e.g. IFN-alpha, IL2.
  - BCG therapy.
  - Cell therapy.

Passive Immunotherapy

- It is comprised of antibodies and other immune system component that are made outside the body and administered to the patient to provide immunity against the disease. It do not stimulate a patient immune system to actively respond to a disease in the way vaccines does.

Types of Passive Immunotherapy

- Monoclonal antibodies therapy
- Cytokine inhibitors
- IV immunoglobulin
- Immunosuppressants
- Haemopoitic stem cell transplantation

* Monoclonal Antibody Therapy

Types:

- Naked monoclonal antibodies, e.g. cetuximab; trastuzumab
- Conjugated monoclonal antibodies, antibodies contain immunotoxin e.g. gemtuzumab
- Radio-labelled antibodies e.g. tositumomab
- Chemo-labelled antibodies e.g. brentuximab

* Cytokines Inhibitors

These are cytokine specific substance that inhibit the biological activities of specific cytokines in a number of different ways:

- Production can be blocked e.g. etanercept
- Intracellular process which produce the active protein can be inhibited
- Cytokines can be neutralized in the circulation e.g. infliximab
- Specific receptor can be blocked e.g. kineret

* IV immunoglobulins

- It contains the pooled human immunoglobulins (95% IgG) extracted from the plasma of over one thousand blood donors.
- IV IG's effects last between 2 weeks and 3 months.
- It is mainly used as treatment in three major categories:
  - Immune deficiencies .
  - Autoimmune diseases
  - Acute infections.
- Its use in SLE: mainly immune thrombocytopenia, and nephritis, mucocutaneous manifestations or arthritis

- IV IG mechanism of action:
  - Modulates Fc receptors function, suppresses antibody synthesis (mononuclear or polynuclear phagocytes)
  - Inhibition of complement consumption and activation by pathogenic antibodies
  - Interference with T cell regulation and cytokine release
  - Feedback inhibition of autoantibody synthesis by auto-reactive B cells
  - Unlike cytotoxic drugs IV IG provides defense against infection

IV IG dose:

- Dosage of IV IG is dependent on indication.
- For primary immune dysfunction 100 to 400 mg/kg of body weight every 3 to 4 weeks is implemented.
- For neurological and autoimmune diseases:
  - Total dose of 2 g/kg of body weight used either 1g/kg/day for 2 days, or 0.4g/kg/day (400 mg/kg/day) for 5 consecutive days.
  - Reconstitute in D5W or NS (avoid foaming) over 20 minutes.
  - Pre-medicate with acetaminophen and diphenhydramine
  - Then maintenance therapy of 100 to 400 mg/kg of body weight every 3 to 4 weeks follows.

Complications of use of IV IG:

- Anaphylaxis (esp. in IgA defient)
- Fever, chills, back pain (48-72 hours after infusion)
- Aseptic meningitis
- Increased viscosity and thromboembolism

* Immunosuppressants

- Glucocorticoids.
- Calcineurin inhibitors:
  - Cyclosporine
  - Tacrolimus
- Antiproliferative / antimetabolic agents:
  - Sirolimus
  - Everolimus
  - Azathioprine
  - Mycophenolate Mofetil
  - Others: Cyclophosphamide, methotrexate, thalidomide and chlorambucil

- Antibodies:
  - Anti-thymocyte globulin
  - Anti CD3 monoclonal antibody : Muromonab
  - Anti IL-2 receptor antibody : Daclizumab, basiliximab
  - AntiTNF alpha: infliximab, etanercept

Other Immunosuppressants

- Non Specific immunosuppressants:
  UV, Plasmapharesis, Photopharesis.
- Biologic Response Modifiers

OTHER THERAPIES USED IN SLE

NSAIDs

Hydroxychloroquine (Plaquenil):

- B hydroxylated chloroquine
- Less ocular toxicity than chloroquine
- Concentrates in lysosomes and has anti inflammatory properties
- High uptake in melanine-containing tissues:
  - Epidermis and Retina
- Metabolized by the liver and excreted by kidneys
- Dose: 200 mg/day, could be increased to 200mg twice daily after 1 week
- Toxicity:
  - Retinal; baseline occular examination, then annular screening
  - GI toxicity

Glucocorticoids

Mechanism of action:

- ✓ Induce redistribution of lymphocytes-decrease in peripheral blood lymphocyte counts
- ✓ Intracellular receptors-regulate gene transcription
- ✓ Down regulation of IL-1, IL-6
- ✓ Inhibition of T cell proliferation
- ✓ Neutrophils, Monocytes display poor chemotaxis
- ✓ Broad anti-inflammatory effects on multiple components of cellular immunity

Modes of Administration of Corticosteroids:

- Intra-articular or intralesional
- Oral therapy
- Parenteral: intravenous, (or +/- IM)

Uses of Glucocorticoids in SLE:

- **Regimen 1:**
  - Daily oral short-acting (prednisone, prednisolone, methyleprednisone) 1-2 mg/kg daily
  - Begin in divided doses then consolidate to single daily dose
  - It controls disease rapidly:
    - 5-10 days for hematologic, CNS disease, serositis or vasculitis
    - 2-10 wks for glomerulonephritis

- **Regimen 2:**
  - Intravenous methylprednisolone 500-1000 mg every day for 3-5 days
  - Then 1-1.5 mg/kg /day of oral glucocorticoids
  - life-threatening situations such as: rapidly progressive renal failure, active CNS disease, severe thrombocytopenia, alveolar hemorrahge…etc.
  - It controls disease rapidly, probably more rapidly than daily oral therapy. A few non responders to regimen 1 respond to regimen2

- **Regimen 3:**
  - Combine regimen 1 or 2 with cytotoxic or other immunosuppressive therapy

➢ Scheme for Pulse steroid:

- 10-30 mg/ kg of methylprednisolone (500-1000 mg/ dose) is given IV with dextrose 5% in water, normal saline or dextrose 5% in 0.45% sodium chloride, over 30 minutes for three to six days. Then maintaining response with high doses oral prednisone 40-60 mg/day, which are rapidly tapered.

- Repeat 1 to 3 days a month is an acceptable alternative to addition of cytotoxic drugs

- Patients who do not show improvement with this regimen probably are unresponsive to steroids, and other therapeutic alternatives must be considered

Glucocorticoid toxicity

- Growth retardation
- Avascular Necrosis of Bone
- Risk of Infection
- Poor wound healing
- Cataract
- Hyperglycemia
- Hypertension
- HPA axis suppression

- To minimize the risk of HPA axis suppression, glucocorticoids should be taken before 10: 00 AM (circadian rhythm with peak level in the morning). This will have less suppressive effect on the release of cortisol-releasing factor.

- Moreover, dosage scheduling will affect the adrenal suppression, from the least to most suppressive, these are:

  - Alternate day (single dose every other morning)
  - Single daily AM dose
  - Intermittent intravenous pulse therapy
  - Multiple daily dosing

Calcineurin inhibitors

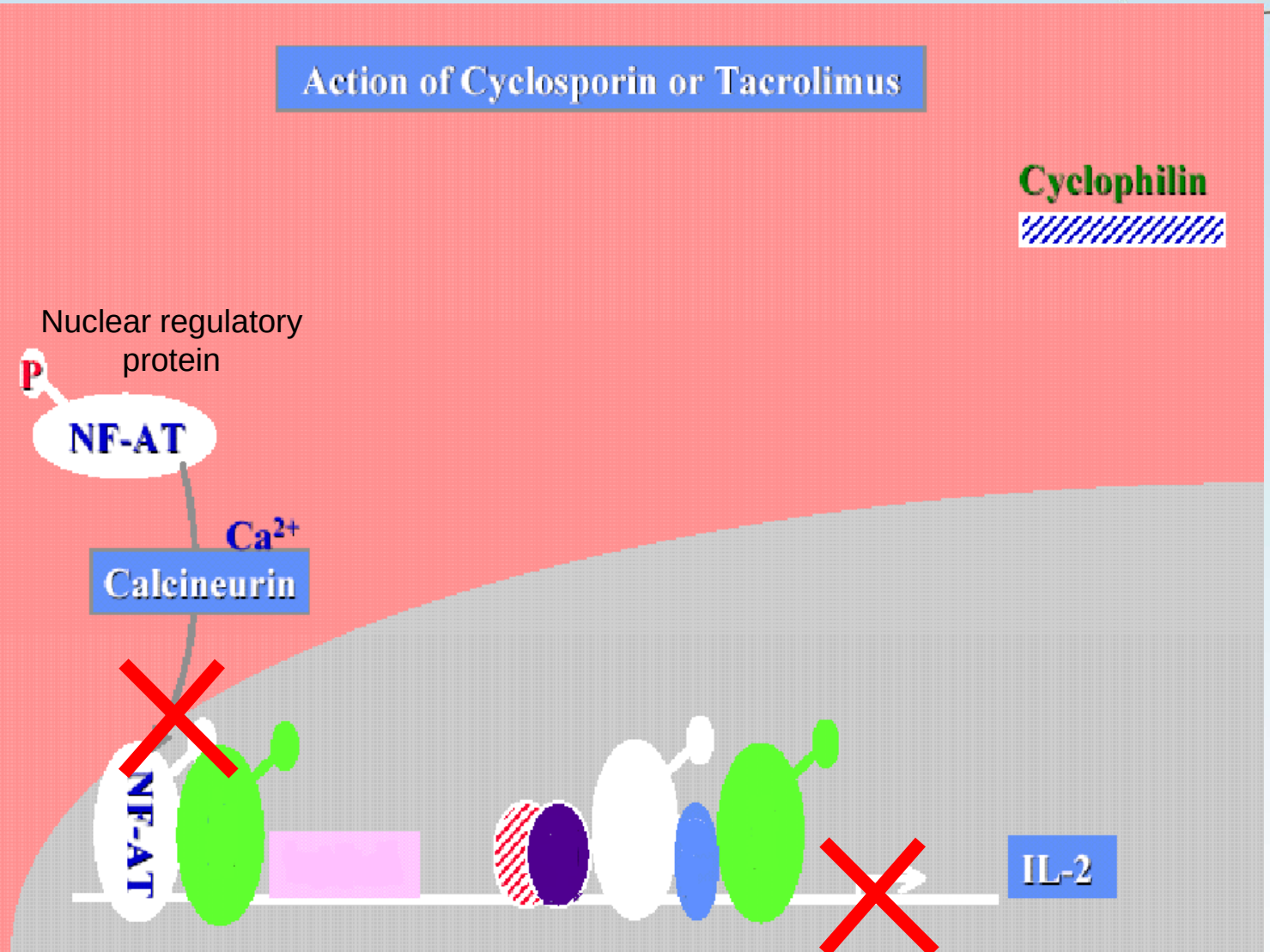
- Cyclosporine (Neoral, Sandimmune)
- Tacrolimus (Prograf)
  - Most effective immunosuppressive drugs
  - Target intracellular signaling pathways
  - Blocks Induction of cytokine genes

Cyclosporine (Neoral)

Mechanism of action:

- cyclosporine binds to cyclophilin → cyclophilin/cyclosporine complex → binds calcineurin → no cytokine production.
- It inhibits T cell mediated response
- More effective against T-cell dependent immune mechanisms: transplant rejection, autoimmunity
- Route : IV, Oral
- Dose: 2.5-5 mg/kg/day, improves proteinuria, cytopenias and immunological parameters.
- Used in membranous nephritis (class V).

Inhibits IL-2 and IL-2 receptor expression
Prevents lymphocyte proliferation –
Cells arrested in G0/G1



Toxicity of Cyclosporine:

- Renal dysfunction
- Tremor
- Hirsuitism
- Hypertension
- Hyperlipidemia
- Gum hyperplasia
- Hyperuricemia, worsens gout
- Calcineurin inhibitors + Glucocorticoids= Diabetogenic

Tacrolimus

Mechanism of action:

- Tacrolimus is Macrolide antibiotic compound, it binds to tacrolimus binding protein (FKBP) → complex → binds calcineurin → no cytokine production
  = (Inhibits T-cell activation by inhibiting calcineurin)

Toxicity:

- Nephrotoxicity
- Neurotoxicity-Tremor, headache, motor disturbances, seizures
- GI Complaints
- Hypertension
- Hyperglycemia
- Risk of tumors, infections

Antiproliferative & Antimetabolic Drugs

- Sirolimus
- Everolimus
- Azathioprine
- Mycophenolate Mofetil
- Others:
  - Cyclophosphamide
  - Methotrexate
  - Thalidomide
  - Chlorambucil

Sirolimus

Mechanism of action:

- Inhibits T-cell activation and proliferation
- Complexes with an immunophilin, Inhibits a key enzyme in cell cycle progression - mammalian target of rapamycin (mTOR)

Uses

- Prophylaxis of organ transplant rejection along with other drugs

Toxicity

- Increase in serum cholesterol, triglycerides
- Anemia
- Thrombocytopenia
- Hypokalemia
- Fever
- GI effects
- Risk of infection, tumors
- Drug Interactions: CYP 3A4

Everolimus

- Shorter half life compared to sirolimus
- Shorter time taken to reach steady state
- Similar toxicity, drug interactions

Azathioprine (Imuran)

Mechanism of action:

Is a purine analogue inhibits nucleic acid synthesis, so affecting cellular and humoral immunity:

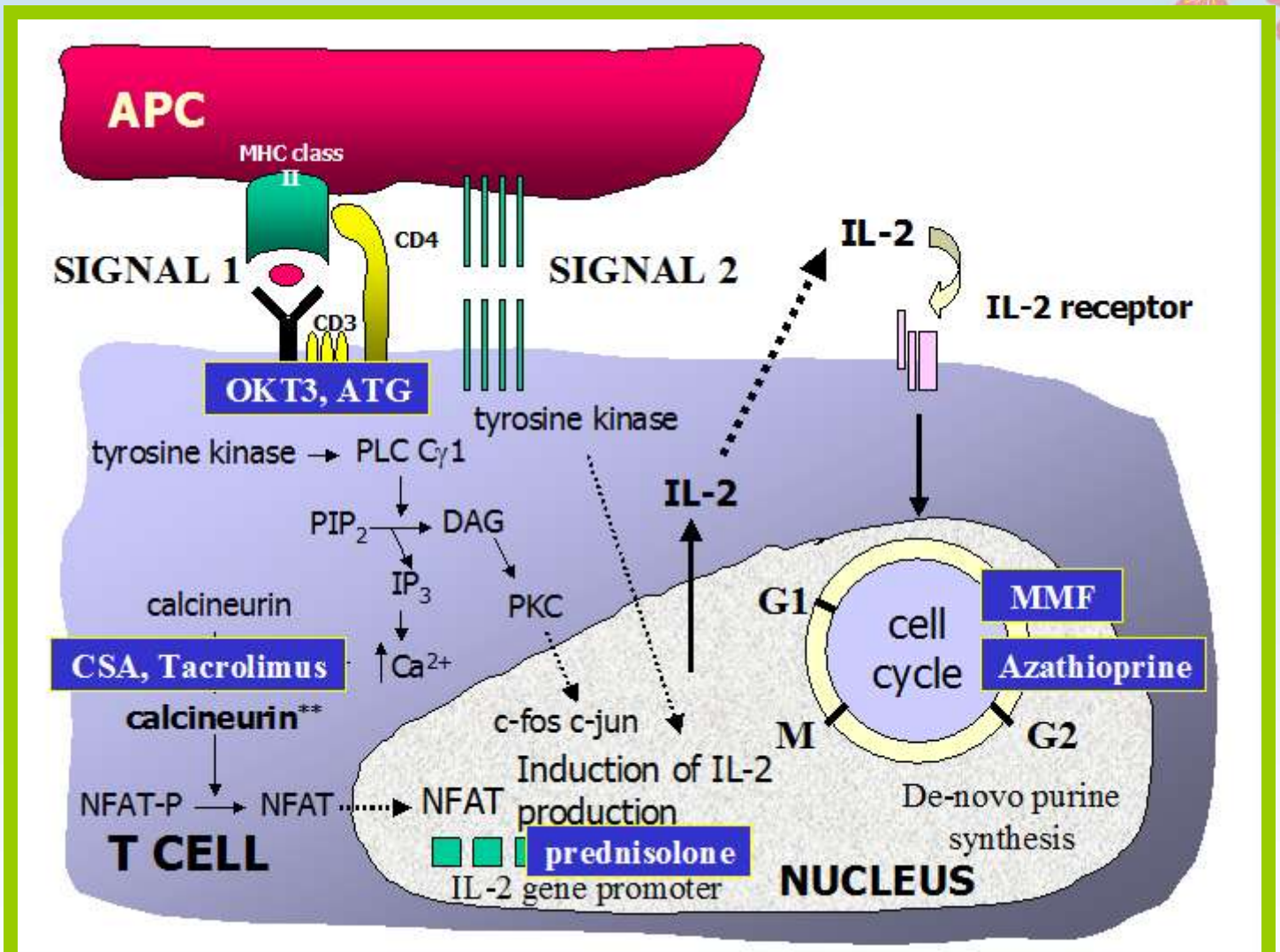
- Purine anti-metabolite, metabolized to 6-mercaptopurine by red cell glutathione.
- 6-MP metabolized by xanthine oxidase and thiopurine methyle transferase, so co-adminstration with allopurinol is CI
- Inhibition of cell proliferation
- Impairment of lymphocyte function

Doses:

- 2mg/kg per day, oral. Starting dose 50mg PO/day, increased by 25mg/day every 1-2 weeks after CBC
- After final dose, CBC every 4-6 weeks

How Cytotoxic Drugs Work?

Kill dividing cells; interfere with DNA & RNA synthesis:



Toxicity:

It has a fewer side effects than cyclophosphamie and could be considered in treatment of focal proliferative nephritis (WHO class III).

- Bone marrow suppression- leucopenia, thrombocytopenia, anemia
- Live vaccines are CI, influenza/pneumococcal vaccine encouraged.
- Increased susceptibility to infection
- Hepatotoxicity
- Alopecia
- GI toxicity
- Lymphoma

Mycophenolate Mofetil (CellCept)

Mechanism of action:

- Inhibits inosine monophosphate (IMP) dehydrogenase which is a critical enzyme in purine synthesis; results in reduced B and T lymphocyte proliferation and antibody production.

Dose:

Used in cyclophosphamide resistant nephritis

- 1.5-3 gm daily given BID to TID.
- Initiate with 500 mg PO daily; evaluate for BM toxicity (CBC), or GI intolerance.
- Increase by 500mg each time, monitoring CBC
- Well tolerated dose is 500-1000mg twice daily

Toxicity:

- Immunosuppression
- Marrow toxicity
- GI toxicity
- Increase lymphoma risk

Mycophenolic acid (Myfortic) is better tolerated than MMF (360 mg dose equivalent to 500mg MMF)

Cyclophosphamide (Endoxan)

- Alkylating agent
- Depletes B and T cells
- Liver metabolism to:
  - 4-OH-cyclophosphamide
  - Phosphoramide mustard (active ingredient)
  - Acrolein (bladder toxicity)
- Renal excretion within 48 hours

Dosing for pulse IV therapy:

- Initiate at 750 mg/m2, dose is reduced to 500mg/m2 if cr. clearance < 30 ml/min.
- Nadir WBC 7-14 days after dose:
  - if WBC < 1.5 k, reduce dose by 25%
  - If WBC > 4.0k, increase dose (max 1000mg/m2)

- Trimethoprime-sulfamethoxathole daily prophylaxis is indicated mainly in oral daily dosing.

Protocol of IV pulse therapy:

- Mix in 150 ml normal saline or D5W given over 60 minutes.
- MENSA (is acrolein binder) in 20% of total cycl. dose, immediately before and every 3 hours for a total of 4 doses
- Dexamethasone 10 mg orally 3-4 hours after cyc.
- Hydration with D5 ½ NS at 150-200 ml/h for total of 2-4 liters.
- Drink fluid (2 liters) for the rest of the day
- Bladder irrigation may be used if the patient unable to tolerate IV fluids

Cyclophosphamide daily oral therapy

- Initial dose 50 mg daily in the AM with 1 liter of fluid throughout the AM
- Increase every 7-14 days after CBC
- Final dose 1-2 mg/kg/day
- CBC ever 4-6 weeks thereafter
- Trimethoprime-sulfamethoxathole daily prophylaxis
- Combined with corticosteroid to prevent progressive renal scarring, used in class IV nephritis

- Toxicity:
  - Infiltration causes extensive tissue necrosis
  - Hemorrhagic cystitis and bladder cancer
  - Immunosuppression, opportunistic infection
  - Hematopoietic Mg
  - Infertility (common)
  - Hepatitis
  - GI toxicity
  - Alopecia
  - Teratogenic

Methotrexate:

- Less effective role in SLE in comparison to RA
- Cutaneous and musculoskeletal manifestations of SLE are the most responsive to MTX
- Dose: 15-20 mg/weak could control disease activity.
- Considered one of the steroid-sparing drugs, as azathioprine and plaquenil.
- Toxicity:
  - Increased liver enzymes
  - GI toxicity
  - Infection

Antibodies

- Against lymphocyte cell-surface antigens
- Polyclonal / Monoclonal
  - Anti-thymocyte globulin
  - Anti CD3 monoclonal antibody: Muromonab
  - Anti IL-2 receptor antibody: Daclizumab, basiliximab
  - Anti-TNF alpha: infliximab, etanercept

Anti-thymocyte Globulin

Mechanism of action:

- Purified gamma globulin from serum of rabbits immunized with human thymocytes
- Cytotoxic to lymphocytes & block lymphocyte function

Uses

- Induction of immunosuppression
- transplantation
- Treatment of acute transplant rejection

Toxicity

- Hypersensitivity
- Risk of infection, Malignancy

Anti-CD3 Monoclonal Antibody

- Muromonab-CD3
- Binds to CD3, a component of T-cell receptor complex involved in:
  - antigen recognition
  - cell signaling & proliferation
  - Induce rapid internalization of T cell receptor, so preventing subsequent antigen recognition

Uses of Anti-CD3 Monoclonal Antibody

- Treatment of acute organ transplant rejection

Toxicity

- "Cytokine release syndrome"
- High fever, chills, Headache, tremor, myalgia, arthralgia, weakness

Campath-1H (Alemtuzumab)

Mechanism of action:

- Targets CD52
- expressed on lymphocytes, monocytes,Macrophages
- Extensive lympholysis
- Prolonged T & B cell depletion

Uses

- Renal transplantation